PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Donald MORTON,
Rishab K. GUPTA and
David M. EUHUS

Serial No.: 07/431,533

Filed: November 3, 1989

For: URINARY TUMOR ASSOCIATED ANTIGEN, ANTIGENIC SUB-UNITS AND METHODS OF DETECTION

Group Art Unit: 1806

Examiner: M. Davis

Atty Dkt.: CADL:002/SLH

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REPLY BRIEF

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REPLY BRIEF

BOX AF
Commissioner of Patents
Washington, D.C. 20231

Sir:

Appellant hereby submits an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer mailed on February 13, 2001. This reply is due on April 13, 2001. Also accompanying this brief is a Request for Oral Argument, and the fees required therefor. No other fees are believed due; should any other fees be due, or the attached petition fee be deficient or absent, the Commissioner is authorized to withdraw the appropriate fee from Fulbright & Jaworksi Deposit Acct. No. 55-1212/10005391/SLH. Please date stamp and return the enclosed postcard to evidence receipt of this document.

I. REAL PARTIES IN INTEREST

The real parties in interest remain the inventors, Drs. Rishab Gupta, Dr. David Euhus, and Dr. Donald Morton.

II. RELATED APPEALS AND INTERFERENCE

There are no interferences or appeals for related cases.

III. STATUS OF THE CLAIMS

Claims 1-46 were filed with the original application. Claims 47-79 were added during prosecution. Claims 1-18, 20-61, 67, 68 and 71 have been canceled. ***In addition, in a paper filed on Febuary 14, 2001, claim 19 was canceled.*** Thus, claims 62-66, 69, 70 and 72-79 are pending and stand appeal. A copy of the appealed claims is attached as APPENDIX 1 to this brief.

IV. STATUS OF THE AMENDMENTS

An amendment was filed on February 14, 2001, canceling claim 19. No other amendments have been filed following issuance of the final Office Action.

V. SUMMARY OF THE INVENTION

The present invention is drawn to compositions and methods relating to Urinary Tumor Associated Antigen, or "UTAA." This high molecular weight glycoprotein was initially detected in the urine of melanoma patients, but later found to occur in other bodily fluids. Specification at page 13, lines 6-10. The UTAA has been purified away from other proteins and used to make a monoclonal antibody specific for UTAA. Specification at pages 13-14. Further characterization

reveals a polypeptide subunit of 90-100 kD, with a complexed weight of 590-620 kD under non-reducing conditions. The isoelectric point is 6.1. Specification at page 15, lines 2-17. Also provided are methods for using UTAA to induce or enhance immune response in subjects. Specification at page 16, lines 27-30.

VI. ISSUES ON APPEAL

A. Are claims 62-66, 69, 70 and 72-79 properly rejected under the doctrine of obviousness-type double-patenting over the claims of U.S. Serial No. 08/462,570?

B. Are claims 62, 65 and 73-79 indefinite?

C. Are claims 62-66, 69, 70 and 72-79 obvious over Euhus et al. (Exhibit A); in view of Exley (Exhibit B), Rote et al. (Exhibit C) or Finck et al. (Exhibit D); and Pharmacia (Exhibit E), Ljungquist (Exhibit F), Goldenberg (Exhibit G), and Hofmann (Exhibit M)?

VII. GROUPING OF THE CLAIMS

Claims 63, 64, 66, 69 and 70 stand or fall separately from the other claims with regard to the §103 rejection over Euhus and its supporting references. As explained in detail in the Supplemental Brief, these claims recite particular levels of purity that are not enabled, taught or even suggested by the cited references.

VIII. REPLY

A. The Rejection for Obviousness-Type Double-Patenting

The examiner has again maintained the rejection of all pending claims over claims 14-17 and 48-60 of U.S. Serial No. 08/462,570 for obviousness-type double-patenting. Also, as discussed in the previous brief, the examiner continues to style this rejection as one under §101.

This issue remains unclarified and appellants must assume, given the examiner's reasoning, that it is ***not*** a §101 rejection but, instead, if truly an obviousness-type double-patenting rejection.

Following filing of the supplemental brief, the undersigned became aware of a substantial change in the claims of the '570 case that obviated the reverse rejection for obviousness-type double-patenting over the presently rejected claims. Appellants therefore filed a communication relaying this information via facsimile. Since it appears the examiner did not receive this communication prior to issuing the Examiner's Answer, the substance of that communication is repeated below:

FACTS

1. The obviousness-type double-patenting rejection over the claims of U.S. Serial No. 08/462,570 was first advanced in the Office Action mailed on August 5, 1998. It has been maintained in each of the two subsequent Office Actions.

2. In an Office Action mailed on April 28, 1998, a similar obviousness-type double-patenting rejection was advanced against the '570 application over the claims of the present application. In a response filed on August 21, 1998, all the pending claims of the '570 were canceled and new claims added. It was argued therein that the new claims provided in the August 21st response, and contemporaneous amendments to the present application's claims, obviated that rejection.

3. On April 2, 1999, the examiner in the '570 application withdrew the obviousness-type double-patenting rejection and allowed the case without further amendment.

REMARKS

It is respectfully submitted that, ***if the claims of the '570 application could be allowed over the claims of the present application, then there is no longer any conflict between these two cases.*** In fact, the claims of the '570 application (now issued as U.S. Patent 5,993,828) are all drawn to ***in vivo*** stimulation of immune responses. All but one of the claims of the present application are drawn to compositions of matter, which clearly are patentably distinct from *in vivo* uses. ***Appellants hereby cancel the only other claim, claim 19, without prejudice or disclaimer.*** As such, appellants respectfully

request that the examiner reconsider and withdraw the obviousness-type double-patenting rejection now pending in the present application.

Appellants simply reiterate here that the PTO regularly restricts composition of matter claims from methods, ***particularly in vivo methods***. Thus, in light of the amendments made to the '570 application, and the cancellation of claim 19 of the instant application, the rejection has been overcome. Withdrawal or reversal of the rejection is, therefore, respectfully requested.

B. Rejection Under 35 U.S.C. §112, Second Paragraph

According to the examiner, the claims now are indefinite in the recitation of "substantially" as relates to purification. Appellants traverse. As argued previously, there are a number of distinct indicators of what purity ***can*** be achieved in this systems, including (a) UTAA protein compositions that are purified about 100-fold and 105-fold over UTAA found in urine, (b) UTAA present as at least about 0.6% of total protein in the composition; and (c) UTAA at about 95% and 99.5% free of immunoglobulin.

The examiner's only response is to state that because the degree of purity is not included in the claims, they are indefinite. This is not an argument nor is it reasoning – it is a conclusion. Without any factual or scientific basis for the rejection, appellants submit that the examiner has not carried her burden here. Reversal of the rejection is, again, respectfully requested.

C. The Rejection Under 35 U.S.C. §103

Claims 62-66, 69, 70 and 72-79 stand rejected under §103 over no less than nine references. As appellants have argued repeatedly over the last several years, the cited references fail to provide a sufficient teaching to establish either possession of the subject matter of the

present claims, or a sufficiently enabling disclosure that would permit one of skill in the art to generate such. The latest addition to this group, Hofmann (1987) (Exhibit M), merely provides a disclosure of gel filtration, SDS-PAGE and electroelution of a protein, SVNF, that is totally unrelated to the present invention. As such, this reference in no way addresses any of appellants' prior arguments regarding the deficiencies of the Euhus *et al.* reference, and the lack of information provided by Euhus *et al.*

As stated in the previous brief, Hofmann's contribution at best is to provide a method of making UTAA, which is irrelevant as a matter of law to claims directed to compositions of matter. *In re Bell*, 26 USPQ2d 1529, 1532 ("Finally, the PTO emphasizes the similarities between the method by which Bell made the claimed sequences and the method taught by Weissman. The PTO's focus on Bell's method is misplaced. Bell does not claim an method. Bell claims compositions, and the issue is the obviousness of the claimed compositions, not of the method by which they were made. *See In re Thorpe*, ... 227 USPQ 964, 966 (Fed. Cir. 1985) ....").

The examiner attempts to counter this by arguing that "a product by process is common in the art." Appellants clearly fail to understand this comment. It is especially confusing given that the present claims are not product by process claims. To the contrary, the claims merely reflect physical properties that ensue when the claimed subject matter is subject to certain conditions, such as reducing electrophoresis, heat, or isoelectric focusing. ***The limitations are not product by process limitations***. Thus, it is believed that the cited case law does, in fact, apply here, and in so doing, refutes one of the examiner's primary points – that the availability of technology by which one of skill in the art ***might*** make the present invention is sufficient for

obviousness. As *Bell* and *Paperless Accounting Inc. v. Bay Area Rapid Transit System* establish, this is not the proper standard – there or here.

The examiner also concludes, without any basis whatsoever, that "with a combination of methods taught by Euhus *et al.* and the secondary references, one of ordinary skill in the art would have expected to obtain a protein with the same properties as the claimed UTAA, and having the same degree of purity." As the following points illustrate, nothing could be further from the truth.

1. Parameters Necessary for the Isolation of UTAA from Urine

The examiner argues that the Pharmacia reference teaches how to isolate proteins using ion exchange and gel filtration. This is not contested. The examiner also provides an extensive discussion of how one could use autologous sera to find such antigens once they had been fractionated. However, this clearly is a circular argument and is an essential flaw in the examiner's reasoning. Assuming one could isolate ***some*** fraction containing UTAA, how would one know that they had purified the correct antigen ***or*** the correct antibodies, much less identify a patient that even contained these substances? The answer, of course, is that they could not know since the prior art fails to teach which fraction contained UTAA, or how one could identify UTAA from any other protein using any readily obtainable, well-characterized antibodies.

In the Answer, the examiner doggedly hangs on to this argument and, in so doing, misses the entire point. For example, it is argued that "It is not necessary to use well-characterized antibodies ... because Euhus *et al.* teach that UTAA could be detected by ELISA using autologous or allogenic antibodies." The examiner goes on to admit that "in patient sera, there are several antibodies reacting to proteins other than UTAA," but insists that UTAA could be differentiated from other proteins by molecular weight. This still does not address the following question: ***what if***

the patient being examined had another antigen with a similar molecular weight as UTAA? Without any basis for knowing whether or not a given antigen ***was***, in fact, UTAA, there would be no way of ensuring that the protein being isolated was the one described by Euhus *et al.* Until the examiner answers this question in some meaningful fashion, it is submitted that appellants' position on non-enablement in controlling.

2. Structure and Immunologic Profile of UTAA

The examiner also argues that proteins can be isolated without knowledge of their amino acid sequence. While true generally, this still avoids the critical question of knowing, at the end of the day, what it is one has isolated. The cited prior art merely identifies something called "UTAA," and provides a collection of general techniques that ***might*** purify UTAA, without any indication of how to confirm this or to identify which purified fraction actually contains UTAA. In the Answer, the examiner simply reiterates that "one of skill in the art could obtain a protein which has the same properties as the claimed UTAA ...." Perhaps this is true – perhaps not – but the question remains as to ***whether or not it would be UTAA***. As such, appellants again submit that the examiner's attempted rebuttal misses the point.

3. The Reisfeld Declarations

Appellants have pointed to two declarations (Exhibits H and I) from Dr. Ralph Reisfeld. In his first declaration, Dr. Reisfeld stated that one of skill in the art, upon reading the Euhus abstract, could not expect to reproduce the invention given the scant teachings provided therein due to the absence of key conditions (ionic strength, pH, retention times) under which a successful isolation was to be performed. In his second declaration, Dr. Reisfeld noted that the

abstract also contained no information on the sequence or immunogenic identity of the claimed antigen and, thus, even if it could be isolated, the skilled artisan would not know that the antigen was the same as that claimed.

In rebuttal, the examiner now offers that "specific pH or ionic strength is not required" as "it is well known in the art that a protein could be isolated with a gradient elution using a range of salt of pH concentration ...." Assuming this to be true, appellants' claims are not drawn to "a protein" – they are drawn to UTAA. Thus, without the conditions that results in purification of ***UTAA***, the examiner's comments ***still*** miss the point – how do you isolate ***UTAA***, not some unspecified "protein," without knowing what conditions permit that isolation? This confusion is highlighted by the examiner's conclusory remark that "a well characterized antibody specific for UTAA is not necessary for detection of UTAA." In fact, ***in the absence of a protein sequence***, appellants submit that a ***publicly available*** antibody specific for UTAA is, in fact, necessary for the ***repeatable*** detection of UTAA.

4. The Shively Declaration

In yet further declaratory support, Dr. John Shively has explained that the Euhus abstract "does not contain sufficient information to enable purification of UTAA," based on the facts that (i) the abstract describes the purification of antigen antibody complexes that contained numerous other species, and (ii) there was insufficient information on how to purify UTAA from this heterogeneous composition. Further, Dr. Shively notes that only in later, post-published papers, were the specific parameters necessary for purification of UTAA finally spelled out.

The examiner responds that "nowhere [*sic*] in the specification do Appellants disclose the identification of sera that are free of immune complex for use in the purification of UTAA, or the

modification of the isolation procedure to isolate UTAA under these circumstances." However, the point is that appellants are in possession of a monoclonal antibody that binds UTAA, and provides an unambiguous identification of that protein. The prior art, to the contrary, provides only vary general discussions techniques which, when performed under certain conditions, might provide UTAA. Thus, even assuming the examiner is correct in her assessment of the present specification, this still has no bearing on appellants' argument that the prior art is not enabling.

5. Individual Teachings of the Secondary References

Finally, the previous brief noted that, while many proteins can be isolated, and antibodies can be produced against many purified antigens, this is not enablement for UTAA. Similarly, ion exchange chromatography or gel filtration themselves are valuable tools, but the disclosure of such techniques cannot provide, in isolation, at repeatable teaching of purified UTAA. The examiner argues that "the secondary references are recited to teach in details [*sic*] the routine methods of purification of UTAA as taught by Euhus *et al.*" The point, however, is that these secondary references ***do not*** teach the details of purification of UTAA, they address other proteins, or proteins in general, neither of which are relevant to the issue at hand – whether the prior art enables purification of UTAA.

6. Claims 63, 64, 66, 69 and 70 are Separately Patentable

Claims 63, 64, 66, 69 and 70 are drawn to various levels of UTAA purity. For example, claims 63 and 66 discuss "-fold" purification over UTAA found in urine, claim 64 discusses the percent total protein of UTAA, while claims 69 and 70 refer to a percent absence of immunoglobulin. The examiner has simply glossed over these limitations in the claims in

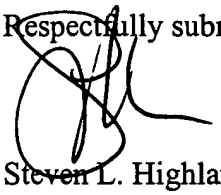
arguing that one of ordinary skill in the art would expect the same result given that both the present specification and Euhus *et al.* used gel filtration, and because "purification from Ig's other than IgG and IgM is not an issue for [the] 103 rejection here."

The examiner again misses appellants' point. Euhus *et al.* is a "black box" when it comes to purification of UTAA. It provides no information whatsoever on what ***kind*** of gel filtration was used, and provides no repeatable method for immune purification. To the contrary, the present application enables a variety of methods by virtue of its disclosure of an anti-UTAA monoclonal antibody. Thus, even if true that the specification did not demonstrate particular levels of purity, which appellants' contest, the issue remains that the present application ***enables such***, while Euhus *et al.* does not.

IX. CONCLUSION

It is respectfully submitted, in light of the above, all pending claims are non-obvious over the cited references. Therefore, appellants again request that the Board overturn the pending grounds for rejection.

Respectfully submitted,



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Date: April 12, 2001

APPENDIX 1 -- PENDING CLAIMS

62. An antigen composition comprising a substantially purified tumor antigen, wherein the tumor antigen is identified as comprising Urinary Tumor Associated Antigen (UTAA) subunit which, after reduction by ß-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD, and wherein said subunit contains glycosidase-sensitive carbohydrates, is heat stable at 100°C, and has an isoelectric point of about 6.1.

63. The antigen composition according to claim 62, wherein UTAA is purified at least about 100-fold over UTAA found in urine.

64. The antigen composition according to claim 62, wherein said UTAA is present as at least about 0.6% of total protein in said composition.

65. The method of claim 19, wherein said method comprises enhancing in a subject the production of antibodies reactive with UTAA.

66. The composition of claim 63, wherein said UTAA is purified 105-fold over UTAA found in urine.

69. The composition of claim 62, wherein said UTAA is about 95% free of immunoglobulin.

70. The composition of claim 62, wherein said UTAA is about 99.5% free of immunoglobulin.

72. The method of claim 65, wherein the observed enhancement of antibody production is about 2- to 5-fold.

73. A pharmaceutical composition comprising (i) an antigen composition comprising a substantially purified tumor antigen, wherein the tumor antigen is identified as comprising Urinary Tumor Associated Antigen (UTAA) subunit which, after reduction by β-mercaptoethanol and separation by SDS-polyacrylamide gel electrophoresis, exhibits a molecular weight of about 90 to 100 kD and (ii) a pharmaceutical buffer.

74. The pharmaceutical composition of claim 73, wherein said antigen composition is present as at least about 0.63 µg/ml of buffer.

75. The pharmaceutical composition of claim 74, wherein said antigen composition is present as at least about 1.4 µg/ml of buffer.

76. The pharmaceutical composition of claim 75, wherein said antigen composition is present as at least about 36 µg/ml of buffer.

77. The pharmaceutical composition of claim 76, wherein said antigen composition is present as at least about 40 μg/ml of buffer.

78. The pharmaceutical composition of claim 77, wherein said antigen composition is present as at least about 100 μg/ml of buffer.

79. The pharmaceutical composition of claim 78, wherein said antigen composition is present as at least about 200 μg/ml of buffer.

APPENDIX 2 -- EXHIBITS